

Review articles

African Swine Fever Virus: a new old enemy of Europe

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ABSTRACT. African swine fever (ASF) is a highly contagious viral disease of swine with a mortality rate approaching 100 percent. African Swine Fever Virus (ASFV) is a double-stranded DNA virus with a complex molecular structure. Its large genome, encoding multiple virulence factors, allows for efficient replication, which takes place predominantly in the cytoplasm of monocytes and macrophages. Also, ASFV has the ability to interfere with cell signalling pathways, which leads to various modulations in the synthesis profiles of interferon and other cytokines. Sustained viremia favours the persistence of virions in blood and tissues of the convalescents, and the extended circulation of ASFV within the herd. ASFV has been spreading in the Caucasus since 2007, and in 2014 reached the eastern territory of the European Union. Outbreaks pose an economical threat to native pig rearing, especially since a single point source may easily develop into an epizootic event. There is currently no effective vaccine nor treatment for ASF, and eradication is possible only by prevention or the slaughter of diseased animals. This review paper summarizes the current state of knowledge about ASFV.

Key words: African Swine Fever Virus, cell biology, epidemiology, immunology, ticks

Introduction

African Swine Fever Virus (ASFV) is the only member of the Asfarviridae family, genus *Asfivirus*. ASFV is a large enveloped double-stranded DNA virus with an icosahedral morphology. Its genome varies in length from about 170 to 193 kbp (kilobase pairs) depending on isolate [1–3] and contains hairpin loops and terminal inverted repetitions [4,5].

ASFV is a causative agent of African swine fever (ASF), a highly contagious haemorrhagic disease of swine. ASF was first described in Kenya in 1921. Since then, ASFV has been present in Africa, especially in the sub-Saharan region (Fig. 1), where it is still maintained within the wildlife and domestic pig populations [6]. In the second half of the 20th century, ASFV was introduced into Europe (Fig. 2) and the Americas, and although it was eradicated in these areas, the disease remains endemic on the island of Sardinia.

In 2007 ASFV emerged in Europe for a second time following a single introduction into Georgia in the Caucasus [7]. Several other Eurasian and Eastern European countries, i.e. Armenia, Azerbaijan, Iran, Russia, Ukraine, Belarus, Poland and Lithuania, have been affected by ASF between 2007 and 2014 [8–10]. This epizootic incident, which probably originated from an inappropriate African pork waste disposal in Georgia, appears to have spread further into the west of Europe together with the movement of infected wild boar and/or illegal transport of live pigs or pig products [7].

Transmission of ASFV

There are two major groups of organisms that are prone to ASFV infections: suids and soft ticks of the genus *Ornithodoros*. ASFV can multiply in both of these groups [6]. Amongst the Family Suidae, only domestic pigs (*Sus scrofa domestica*), and wild

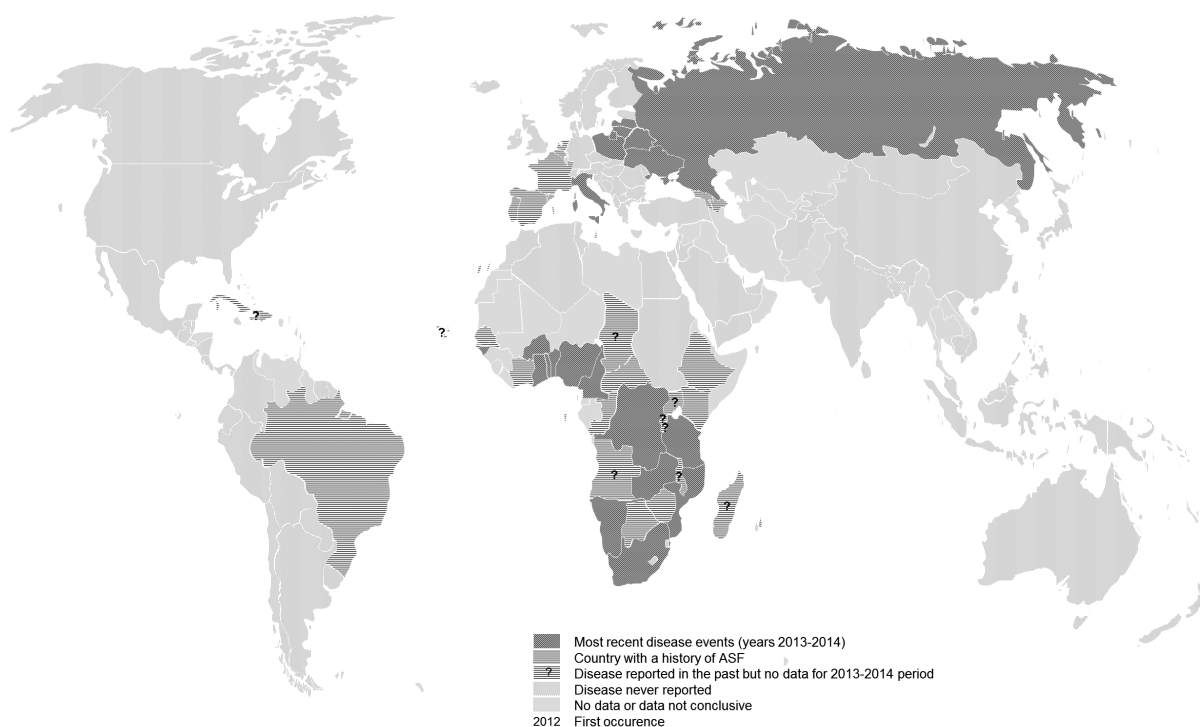


Fig. 1. The incidence of ASFV in the world

boar (*Sus scrofa*) demonstrate clinical signs of infection. In domestic pigs, the mortality rate may be as high as 100% [6], whilst nearly 10% of infected wild boars may not display any clinical signs [11]. Wild pigs, i.e. *Phacochoerus aethiopicus*, *Phacochoerus africanus*, *Potamochoerus* sp., and *Hylochoerus meinertzhageni*, are reservoir hosts of ASFV in Africa, despite demonstrating no apparent signs of disease (asymptomatic infection).

ASFV is the only known DNA virus that might be transmitted by arthropods, i.e. by *Ornithodoros erraticus* in Southern Europe, and *O. moubata*, *O. porcinus domesticus*, and *O. porcinus porcinus* in Africa; none of them are present on the territory of Eastern Europe. In *Ornithodoros* this arbovirus (arthropod borne virus) is easily transferred from one tick organism to another, and the transmission occurs by transstadial, transovarial or sexual passage [6]. Ticks may then transmit the virus into the porcine organism and *vice-versa*. Transmission in suids progresses in a herd of swine with or without tick mediation. Pigs with an ongoing disease, convalescents and wild, apparently uninfected suids act as reservoirs of ASFV. It has been noted that in older wild suids, the virus titre in the blood may not become high enough to infect ticks and mammals [12]. The main sources of ASFV are the tissues and blood of infected animals,

regardless of their health condition; however, the virus titre in faeces, saliva or urine is low. Additionally, household food waste containing undercooked pork products can contribute towards the spread of the virus through consumption by pigs. Another indirect route of infection is through contact with contaminated implements, clothes and vehicles [6]. Suid infection occurs in the closest lymph nodes via the nasal/oral cavity, the pharyngeal mucosa and tonsils [12].

Clinical signs of ASF

Although the disease caused by ASFV may have a peracute, acute, subacute or chronic form, the acute form with haemorrhagic fever is most common. Symptoms typically become apparent three to 15 days following exposure; however, as the acute form has an incubation period of three to four days, infected animals may die before observation of any clinical signs. Infections caused by highly virulent strains of ASFV, like those found in the Caucasus and Eastern Europe, are characterized by sudden deaths with few clinical signs of infection. In their acute form, symptoms include high fever (40.5–42°C), a fall in the number of total white blood cells and thrombocytes within 48–72 hours, increased pulse and respiratory rate, vomiting,

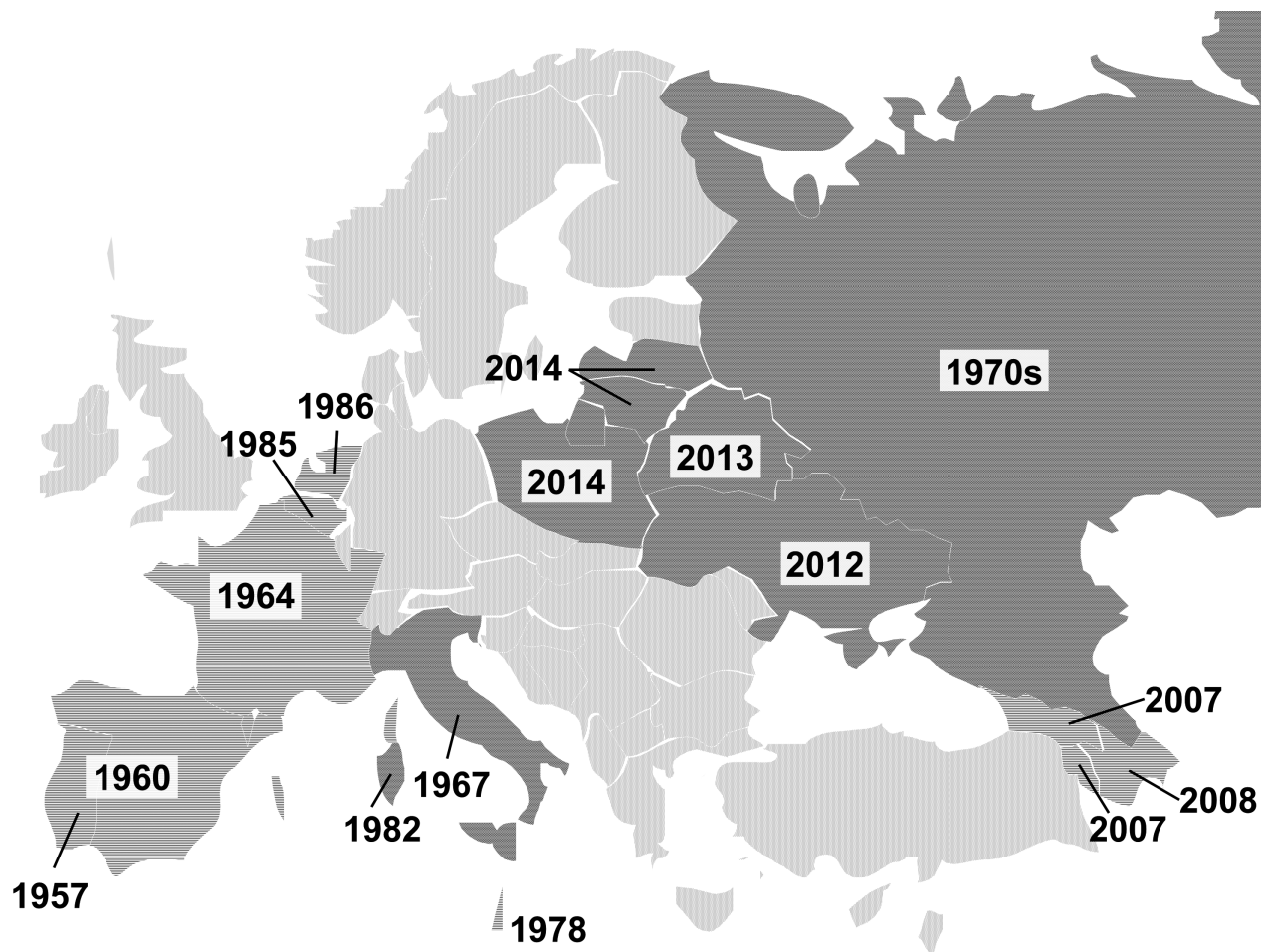


Fig. 2. The incidence of ASFV in Europe

diarrhoea, eye discharges and a reddening of distal extremities, chest and abdomen, as well as cyanosis, anorexia and listlessness. Animals infected with acute ASF also present lesions, especially in the lymph nodes, kidneys, bladder, spleen and the mucous membranes of visceral organs, with these usually being of a petechial character. This form of ASF leads to the death of 100% of infected domestic pigs in six to 13 days, although this can be extended to twenty.

Less intense signs are noted for the subacute form, which is associated with a mortality rate of between 30% and 70% in domestic pigs. The chronic form develops over five to 12 months. The signs of chronic infection are seen mainly in the skin (necrosis, ulcers), joints (swellings, inflammation), pericardium and lungs, and are associated with loss of weight and irregular peaks of temperature. Lesions are less evident, with enlargement of lymph nodes and the necrosis and mineralization of the lungs being found [13].

Diagnosis of ASF

The differentiation of ASF from other swine diseases with similar clinical signs, i.e. classical swine fever (CSF), porcine dermatitis and nephropathy syndrome (PDNS) and porcine reproductive and respiratory syndrome (PRRS), requires rapid, reliable, sensitive and specific detection methods. Clinical signs of ASFV infection, for example high fever, haemorrhage and generalized reddening of the skin, and such post-mortem features as congestion and enlargement of the spleen and generalized haemorrhage of the lymph nodes, liver and kidney are indistinguishable from those associated with CSF infection. In addition, emaciation, swollen joints, respiratory problems and other signs of chronic disease are also potentially confusing [14].

A dependable diagnosis of ASFV infection starts with the collection of samples: blood with anticoagulant (EDTA), serum, kidney, lung, lymph nodes and spleen [13]. Nowadays, a range of

diagnostic methods are available based on virological (virus or viral proteins), molecular (viral DNA) and serological (antibodies) techniques designed to detect and identify ASFV: immunoblotting, polymerase chain reaction (PCR) and sequencing, enzyme-linked immunosorbent assay (ELISA), haemadsorption test (HAD), fluorescent antibody technique (FAT) and the indirect fluorescent antibody test (IFA). The first three are most frequently used. For the initial diagnosis, it is recommended that at least two different tests are performed [13]. The PCR technique is a sensitive, specific and rapid method, with much higher sensitivity and specificity than other techniques such as antigen ELISA and FAT assays. Real-time PCR has recently emerged as the 'gold standard' test for detection of viral DNA. An undeniable advantage of this method is the potential for automation, which may lead to the increase in the sample throughput and decrease the possibility of cross-contamination [14]. Still, recommendations involve both the virus and the antibodies detection [13].

Vaccine

There is still currently no vaccine for African swine fever. In Europe, excluding Sardinia, the disease is controlled by animal quarantine and slaughter, while in South America/Caribbean, drastic control and eradication programs are used to suppress the spread of the infection [15]. The main reason why vaccines do not work is the lack of production of neutralizing antibodies by the infected host; in addition, the virus is highly complex with regard to its large size, structure and multiple virulence factors, and it has a heterologous nature which makes the production of vaccines technically difficult. In addition, since ASFV was viewed as an 'exotic' infectious agent in developed countries, no adequate attempt has been made to find an appropriate vaccine [16].

A range of strategies have been used so far, with one based on the use of inactivated virus. However, in spite of the fact that they were able to induce response of antibodies, they did not offer effective protection. Although vaccines based on attenuated strains were capable of presenting a durable defence against the homologous viral strains and, rarely, against heterologous viruses, their application was thwarted by safety issues since attenuated vaccines still produced sub-clinical and chronic infections.

Subunit vaccines, by contrast, appear to be a safe alternative but only offer partial protection: the vaccination caused a decrease in viremia titres, but similar, mild symptoms such as fever, recumbency and anorexia were still present [16].

Currently, attenuated or non-replicating (in the swine host) viral strains, viral DNA and protein mimicking peptides are very promising candidates for vaccines against ASF. Immunization with a vaccine containing a plasmid encoding viral antigens (p54, p30) and the extracellular domain (hemagglutinin) induces partial protection against ASFV characterised by the expansion of CD8+ T cells with an absence of antibodies [16]. In addition, the peptide-based vaccine significantly delayed mortality in domestic pigs infected with ASFV [17]. Nevertheless, more studies are needed in this field.

Immune response to ASFV infection

The development of ASF may be possible only due to viral-induced alterations in the host immune system, to which this virus is well adapted. ASFV infection leads to induction of innate and adaptive immunity [18]. Early host defence mechanisms rely on the interferon (IFN) system [19,20]. IFN synthesis is an innate response to virus entry and takes place long before specific antiviral antibodies are produced. The main classes of type I IFN, i.e. IFN- α and IFN- β , are induced directly in response to the viral infection, resulting in the expression of many antiviral genes that interfere with the virus replication cycle at several levels. Moreover, the release of type I IFN leads to the secretion of large amounts of cytokines that recruit and activate the cells of the innate immune system [18].

ASFV is able to interfere with the signalling pathways responsible for IFN transcription. A number of virus proteins prevent the induction of IFN via Toll-like receptor 3 (TLR3) and cytosolic pathways. The A276R protein inhibits the INF- β induction at the level of interferon regulatory factor (IRF), and the ASFV A528R protein interferes with the type I IFN induction signalling pathway by targeting NF- κ B and IRF3 [18]. Another protein, I329L, shows a high level of functional homology to TLR3, and so acts as a TLR3 antagonist, preventing the transduction of IFN-induced signals through targeting Toll-interleukin-1 receptor (TIR)-domain containing adaptor-inducing interferon- β (TRIF). In short, I329L interferes with TRIF as TLR3 homologue [21].

Infection with ASFV also causes changes in the synthesis profiles of other cytokines; for example, a significant increase in the production of interleukins (IL), especially IL-1 β and IL-6, which have pro-inflammatory properties. This effect occurs at the early stage of intracellular infection of porcine macrophages. Early ASFV infection also leads to increases in chemokine concentration, especially in the CC and CXC group [22]. These cytokines act as chemoattractors for immune system cells [23]. ASFV shows a tropism to macrophages and it has the ability to infect them. Therefore, recruitment and activation of these cells promotes viral infection through delivery of the new macrophages intended for viral replication. In addition, ASFV employs macrophages as vehicles to spread throughout the infected organism [24].

Pig hosts that survive the viral infection usually produce antibodies against ASFV between seven and 10 days after infection [25]. Three viral proteins are responsible for inducing the synthesis of specific antiviral immunoglobulins, the first two being p72 and p54. The role of anti-p72 and anti-p54 antibodies in the immune response is to inhibit the virus from attaching to the cells [26,27]. The third highly immunogenic protein of ASFV is p30 (also called p32) [28], whose presence results in the synthesis of specific anti-p30 antibodies. The latter are responsible for virus neutralization through the inhibition of its internalization by the host cells [29].

Cellular pathogenesis of ASFV infection

The replication cycle of ASFV, which is responsible for both cellular pathogenesis during infection and viral assembly, occurs mainly in the cytoplasm of infected monocytes and macrophages, in defined perinuclear factories (viral factories) [30]. Interestingly, although the virus is known to infect other cells including megakaryocytes, platelets, neutrophils and hepatocytes, replication has never been observed in these cells [11]. The initiation of ASFV replication takes place in the nucleus, where it begins between four [31] to six hours post infection (h.p.i.) and falls to almost zero by 12 h.p.i [32,33]. In contrast to the nucleus, the cytoplasmic phase of the viral replication is visible after six h.p.i., following which, its level gradually increases [33].

The role of the early nucleus phase of ASFV replication is not fully understood. However, it is

highly probable that the nucleus may supply important factors or transcripts necessary for the viral replication [34]. Recent findings indicate that ASFV has a number of effects on nuclear organization, including the disassembly of the nucleus lamina network, redistribution of several nuclear proteins, as well as the dephosphorylation and subsequent degradation of the RNA polymerase II [34]. Aside from the nucleus, the presence of ASFV in a cell has been associated with functional disorders in other organelles and cytoskeletal disarrangement [35,36]. These changes in cellular organization are probably related to the regulation of host gene transcription by ASFV and its control of cellular protein synthesis [37].

ASFV is assembled in discrete perinuclear foci called viral factories [30]. These sites are related to other structures named aggresomes, which are also localized near the nucleus and are formed by the cells in response to misfolded proteins [38]. The viral factories and aggresomes are both situated in close proximity to the microtubule organizing center (MTOC) and use the microtubular network for assembly [39]. Both structures cause a rearrangement of the cytoskeleton and the recruited mitochondria and proteasomes, as well as cellular chaperones such as HSP70 [35,39–41]. Hence, it was suggested by Heath et al. [39] that the cellular response against the toxicity of misfolded proteins is exploited by ASFV to concentrate structural proteins at the virus assembly foci. Microtubules can accumulate viral and host proteins, which are required for viral replication or for assembly of the progeny virions, inside the MTOC [42]. In addition, mitochondrial recruitment to ASFV factories is also dependent on microtubules: Studies indicate that these organelles situate around the viral factories and actively respire during ASFV infection, which suggests their role in ATP production is exploited by the virus [42]. In addition, ASFV replication is also known to affect the distribution of endoplasmic reticulum (ER) [43] as well as the redistribution and partial fragmentation of the Golgi apparatus during infection [44,45], which taken together, demonstrates to the extent to which this virus can manipulate the cell.

Conclusions

ASFV is able to modify the functioning of the porcine immune cells and the entire immune system

for its own benefit. The high mortality rate of pigs affected by this virus, and the lack of any effective vaccine are the main reasons why rigorous surveillance is needed by the veterinary services of European countries.

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